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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza I
Suite 1400
2200 Clarendon Boulevard
Arlington, VA 22201

EXAMINER	
KUMAR, SHAILENDRA	

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SCOTT MILLER, MARTIN OSTERHOUT, JACQUES DUMAS, UDAY KHIRE, TIMOTHY BRUNO LOWINGER, BERND RIEDL, WILLIAM J. SCOTT, ROGER A. SMITH, JILL E. WOOD, DAVID E. GUNN, MARTHA RODRIGUEZ, MING WANG, TIFFANY TURNER, and CATHERINE BRENNAN

Appeal 2009-010119
Application 09/776,936
Technology Center 1600

Decided: December 10, 2009

Before TONI R. SCHEINER, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to chemical compounds and a method of treating cancer with them. The Examiner has rejected the compound claims as obvious in view of the prior art, and the

treatment claims as nonenabled. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

The Specification discloses that the "$p21^{ras}$ oncogene is a major contributor to the development and progression of human solid cancers and is mutated in 30% of all human cancers" (Spec. 1: 16-17). "In the ras mutants in cancer cells, . . . the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the cancerous growth of the cells." (*Id.* at 1: 24-26.) The Specification states that "inhibition of raf kinase (by antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human tumor types" (*id.* at 2: 1-3).

Claims 1, 3-11, 13, 15-19, and 21-34 are on appeal.[1] Claims 1, 3-11, 13, 21-27, and 34 are directed to diphenyl ureas defined by structural formulas and claims 15-19 and 28-33 are directed to methods for treating cancerous cell growth mediated by raf kinase using diphenyl ureas defined by similar structural formulas.

The claims stand rejected as follows:

- Claims 1, 3-11, 13, 21-27, and 34 under 35 U.S.C. § 103 as obvious in view of Widdowson[2] (Answer[3] 6); and
- Claims 15-19 and 28-33 under 35 U.S.C. § 112, first paragraph, as nonenabled throughout their full scope (Answer 3).

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[1] Claims 12 and 14 have been allowed (Office action mailed May 3, 2005, page 1).
[2] Widdowson et al., WO 96/25157, published Aug. 22, 1996.
[3] "Answer" refers to the Examiner's Answer mailed Jan. 9, 2009.

OBVIOUSNESS

Issue

The Examiner has rejected claims 1, 3-11, 13, 21-27, and 34 as obvious in view of Widdowson. The Examiner finds that Widdowson teaches "structurally similar compounds, compositions as claimed herein. See for example page 20, lines 15-20, wherein, X1 can be O or S, R2 can be aryl or hetaryl" (Answer 6). The Examiner concludes that the claimed compounds would have been obvious in view of Widdowson's compounds because they are "structurally so similar" and those skilled in the art would have considered it obvious to make positional isomers of Widdowson's compounds (*id.* at 6, 7).

Appellants contend that the claimed compounds "cannot be considered obvious position isomers of the reference's formula Ib since there is no direction or motivation to . . . make all the right choices and selections which are necessary from the reference's generic formula Ib to arrive at a M-L[1] group consistent with this invention and place it at a meta- or para-position on the phenyl group" (Appeal Br.[4] 7).

The issue with respect to this rejection is: Have Appellants shown that the Examiner erred in concluding that the compounds defined by Widdowson's formula 1b would have made the claimed compounds obvious to a person of ordinary skill in the art?

Findings of Fact

1. Widdowson discloses phenyl ureas that are receptor antagonists of interleukin-8 (Widdowson, title and abstract).

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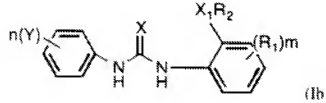
[4] "Appeal Br." refers to the Appeal Brief filed Oct. 16, 2006.

2. One of the genera of compounds disclosed by Widdowson is defined by formula 1b:



(Ib)

(*Id.* at 20: 17-18.)

3. Widdowson discloses that in formula 1b, X and X_1 are oxygen or sulfur (*id.* at 20: 20-21) and "R_2 is a substituted aryl, heteroaryl, or heterocyclic ring which ring has a functional moiety providing the ionizable hydrogen having a pKa of 10 or less" (*id.* at 20: 33-34).

4. Widdowson discloses that suitable functional moieties for the R_2 group include "hydroxy, carboxylic acid, thiol, -NH-C(O)R_a, -C(O)NR_6R_7, substituted sulfonamides of the formula $NHS(O)_2R_b$, -S(O)NHR_c, $NHC(X_2)NHR_b$, or tetrazoyl" (*id.* at 21, ll. 26-29).

5. Widdowson discloses that n and m are 1 to 3 (*id.* at 21: 15-16).

6. Widdowson discloses that R_1 is

> independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C_{1-10} alkyl; C_{1-10} alkyl; C_{2-10} alkenyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; azide; $S(O)_tR_4$; hydroxy; hydroxyC_{1-4}alkyl; aryl; aryl C_{1-4} alkyl; aryloxy; arylC_{1-4} alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic; heterocyclicC_{1-4}alkyl; heteroarylC_{1-4} alkyloxy; aryl C_{2-10} alkenyl; heteroaryl C_{2-10} alkenyl; heterocyclicC_{2-10} alkenyl; NR_4R_5; C_{2-10} alkenyl $C(O)NR_4R_5$; $C(O)NR_4R_5$; $C(O)NR_4R_{10}$; $S(O)_3H$; $S(O)_3R_8$; C_{1-10} alkyl $C(O)R_{11}$; C_{2-10} alkenyl $C(O)R_{11}$; C_{2-10} alkenyl $C(O)OR_{11}$; $C(O)R_{11}$; $C(O)OR_{12}$; $OC(O)R_{11}$; $NR_4C(O)R_{11}$; or two R_1 moieties together may form O-$(CH_2)_s$O- or a 5 to 6 membered unsaturated ring.

(*Id.* at 20: 22-29.)

7. Widdowson discloses that Y is independently selected from the same moieties as R_1 (*id.* at 21: 6-14).

8. Widdowson discloses that "a preferred ring substitution for R_1 is in the 3-position, the 4-position or is preferably di substituted in the 3,4-position. . . . Preferably, R_1 is nitro, halogen, cyano, trifluoromethyl group, or $C(O)NR_4R_5$" (*id.* at 21: 32-35).

9. Widdowson discloses that "[w]hile both R_1 and Y can both be hydrogen, it is prefer[r]ed that at least one of the rings be substituted, preferably both rings are at least mono-substituted" (*id.* at 22: 1-2).

Principles of Law

"Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995).

"An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313 (CCPA 1979).

> Position isomerism is a fact of close structural similarity which is to be taken into consideration with all other relevant facts in applying the test of obviousness under 35 U.S.C. § 103. It is the closeness of the relationship rather than the mere name, or, here, position number, which is significant, and which gives rise to an inference that the claimed compound is obvious.

In re Mehta, 347 F.2d 859, 864 (CCPA 1965) (citations omitted).

Analysis

The Examiner is correct that Widdowson's formula 1b encompasses some compounds that are structurally similar to some compounds that are encompassed by the claims on appeal. But the Examiner oversimplifies the comparison in reasoning that the claimed compounds would have obvious because Widdowson discloses that "X1 can be O or S, R2 can be aryl or hetaryl" (Answer 6): the skilled worker would also need to make appropriate selections for Y, R_1, and the functional group substituted on R_2 in formula 1b, in order to reach a compound that is a positional isomer of those encompassed by the instant claims.

The Examiner has not adequately explained what disclosure in Widdowson or within the knowledge of the skilled worker would have led a person of ordinary skill in the art to choose substituents encompassed by the prior art's formula 1b – for example, for Y, R_1, and the R_2 functional group substituent – that would result in a compound that is a positional isomer of a compound encompassed by the claims on appeal. We agree with Appellants that the Examiner has not shown that it would have been obvious to make the series of choices within Widdowson's formula 1b and then further modify the resulting compound to move the X_1R_2 group to a meta or para position, as required to make a compound encompassed by the claims on appeal.

Conclusion of Law

Appellants have shown that the Examiner erred in concluding that the compounds defined by Widdowson's formula 1b would have made the claimed compounds obvious to a person of ordinary skill in the art.

ENABLEMENT

Issue

The Examiner has rejected claims 15-19 and 28-33 under 35 U.S.C. § 112, first paragraph, as nonenabled (Answer 3). Claims 15 and 16 (the independent claims) are directed to a "method for the treatment of a cancerous cell growth mediated by raf kinase" by administering a dephenyl urea compound similar to those defined by claim 27.

The Examiner finds that, based on the state of the art, it is highly unpredictable whether a given compound will be therapeutically effective in treating cancer (*id.* at 4); that the Specification does not provide a working example of treating a solid tumor with the disclosed compounds (*id.* at 5); that the claims encompass millions of compounds (*id.*); and that each compound must be assessed individually against different types of cancer to determine effectiveness (*id.*). The Examiner concludes that practicing the full scope of the treatment claims would require undue experimentation (*id.* at 5-6).

Appellants contend that they "in the specification teach the compounds of the invention act on raf, teach how the activities of individual compounds can be determined, teach the activities of 144 exemplified compounds from the examples, and provide guidance as to administration modes and amounts throughout the specification" (Appeal Br. 5-6). Appellants also contend that they have provided a working example showing that all of the 144 exemplified compounds inhibit raf kinase, with IC_{50} values between 1 nM and 10 µM (*id.* at 6).

The issue with respect to this rejection is: Have Appellants shown that the Examiner erred in concluding that treating cancerous cell growth

that is mediated by raf kinase, using the compounds encompassed by the claims, would have required undue experimentation?

Additional Findings of Fact

10. The Specification discloses that the "$p21^{ras}$ oncogene is a major contributor to the development and progression of human solid cancers and is mutated in 30% of all human cancers" (Spec. 1: 16-17).

11. The Specification discloses that a mutant ras protein "delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the cancerous growth of the cells." (*Id.* at 1: 24-26.)

12. The Specification discloses that "[i]t has been shown that inhibiting the effect of active ras by inhibiting the raf kinase signaling pathway by administration of deactivating antibodies to raf kinase or by co-expression of dominant negative raf kinase . . . leads to the reversion of transformed cells to the normal growth phenotype" (*id.* at 1: 27-32).

13. The Specification discloses that "inhibition of raf kinase (by antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human tumor types" (*id.* at 2: 1-3).

14. The Specification states that the disclosed compounds "are inhibitors of the enzyme raf kinase. Since the enzyme is a downstream effector of $p21^{ras}$, the instant inhibitors are useful in pharmaceutical compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase." (*id.* at 2: 6-11.)

15. The Specification describes 144 compounds that were synthesized (*id.* at 62-74).

16. The Specification describes an *in vitro* assay for inhibition of raf kinase (*id.* at 74: 3-18) and states that "[a]ll compounds exemplified displayed IC_{50}s of between 1 nM and 10 μM" (*id.* at 74: 20).

Principles of Law

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement.

In re Wright, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993).

"That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). Whether the amount of experimentation required is undue is determined by reference to the factors set out in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

"Enablement does not require an inventor to meet lofty standards for success in the commercial marketplace. Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003).

Analysis

The Examiner points out that the fact that a compound exhibits a particular activity in an *in vitro* assay does not mean that the compound will effectively treat cancer *in vivo* (Answer 4-5). The Examiner's point is well-taken but is not sufficient to support a rejection for nonenablement here. The Examiner does not provide any particularized evidence that specifically demonstrates unpredictability for the claimed raf kinase inhibitors.

The rejected claims are limited to "treatment of cancerous cell growth *mediated by raf kinase*" (claims 15 and 16, emphasis added). The Specification states that the disclosed compound are inhibitors of raf kinase (FF 14), and provides evidence that all 144 exemplified compounds inhibit raf kinase to some degree (FF 15, 16). The Specification also provides a reasoned basis for expecting that compounds that inhibit raf kinase will have the effect of inhibiting the growth of cancerous cells in which the ras gene is mutated (FFs 11-13). Therefore, the Specification provides a reasonable basis for concluding that it enables the method defined by the claims on appeal.

While some experimentation, maybe even a great deal of it, may be required to determine which compounds encompassed by the claims are clinically effective in treating specific types of cancer, that possibility does not preclude enablement. First, enablement for patent purposes does not require providing a clinically effective treatment of cancer. *See CFMT*, 349 F.3d at 1338 ("Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.").

Second, the type and amount of experimentation required to practice the claims on appeal appears to be in line with what would be expected in this art. *See* Answer 4 ("The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compound can treat which specific diseases by what mechanism)."). *See also In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995) ("Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development.").[5]

Conclusion of Law

Appellants have shown that the Examiner erred in concluding that treating cancerous cell growth that is mediated by raf kinase, using the compounds encompassed by the claims, would have required undue experimentation.

SUMMARY

We reverse the rejection of claims 1, 3-11, 13, 21-27, and 34 as obvious based on Widdowson, and the rejection of claims 15-19 and 28-33 for lack of enablement.

REVERSED

[5] Although the *Brana* court referred to "usefulness," the rejection on appeal was for nonenablement. *See* 51 F.3d at 1564.

lp

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
ARLINGTON COURTHOUSE PLAZA I
SUITE 1400
2200 CLARENDON BOULEVARD
ARLINGTON VA 22201